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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/965,131	09/26/2001	Maureen Angela Chung	WII-014CP	1805

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 11/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/965,131	CHUNG ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment and response received on 7/28/03 has been entered. Claim 20 has been amended and new claim 37 has been added. Please note that although the remarks section of the applicant's amendment states that claim 1 has been amended, no actual amendment to claim 1 has been made of record. In the instant response, only claim **20** has been amended and new claim 37 has been added. Claims 1-37 are pending and currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this office action can be found in a previous office action.

Claim Rejections - 35 USC § 112

The rejection of claims 20-24 under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn in view of applicant's amendment to claim 20.

Claim Rejections - 35 USC § 103

The rejection of pending and new claims 1-37 under 35 U.S.C. 103(a) as being unpatentable over Scholl et al. (Sept. 1, 2000) J. Immunother., Vol. 23(5), 570-580 in view of US

Patent. No. 5,776,465 (1998), hereafter referred to as O'Donnell '465, or US Patent NO. 5,591,632 (1997), hereafter referred to as O'Donnell '632, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the office has failed to establish a *prima facie* case of obviousness by failing to provide adequate motivation for combining the teachings of the cited references, citing *In re Rouffet*, *In re Gordon*, *In re Beattie*, and *GMBH v. American Hoist & Derrick Co.* Specifically, the applicant argues that Scholl et al. teaches recombinant vaccinia virus, not a recombinant mycobacterium, and that there is no motivation in either Scholl or the O'Donnell patents to substitute recombinant mycobacterium for recombinant vaccinia virus. To support this argument, the applicant states that Scholl does not make any negative comments about the recombinant vaccinia virus to suggest looking for another organism, and that the motivation to use recombinant BCG over other vaccines does not apply to the recombinant vaccinia virus taught by Scholl because the vaccinia virus taught by Scholl was not "presently available" as of the effective filing date of the O'Donnell patents which applicant states is 1987.

In response, please note that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d

1500 (Fed. Cir. 1988). Case law also states that, "[a]ny judgement on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." *In re McLaughlin*, 443 F2d. 1392, 170 USPQ 209, 212 (CCPA 1971). Finally, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found **either** in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 19880; *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Regarding the instant rejection, the previous office action clearly pointed to the teachings of the O'Donnell patents for motivation for substituting a multivalent BCG for the vaccinia virus taught by Scholl et al. As stated in the previous office action, O'Donnell teaches the construction of a multivalent recombinant BCG vaccine which encodes both an antigen **and** a cytokine, particularly IL-2 (O'Donnell '465, columns 10-11, bridging paragraph, O'Donnell '632, column 11). O'Donnell also teaches that administration of the multivalent BCG vaccine would result in stimulation of an immune response to an antigen as well as a more potent stimulation of T cells and macrophages (O'Donnell '465, column11, lines 2-4, and O'Donnell '632, column 11, lines 23-25). In addition, O'Donnell teaches using the disclosed BCG vaccines for treating cancer (O'Donnell '465, column 11, lines 12-18, and O'Donnell '632, column 11, lines 33-39). Most

importantly, the O'Donnell patents teach that BCG vaccines have important advantages over presently-available vaccines. Specifically, O'Donnell teaches that the adjuvant properties of mycobacteria are the best currently known, that BCG can be used repeatedly, and that BCG immunization results in long-term T cell memory responses and secondary antibody responses (O'Donnell '465, columns 2-3, bridging paragraph, and lines 1-37, and O'Donnell '632, column 3, lines 16-57). Thus, the previous office action makes clear that motivation for combining the teachings of Scholl et al. and O'Donnell can be found in the O'Donnell patents statements regarding the important advantages of multivalent BCG vaccines over other vaccines.

In regards to the applicant's argument that the vaccinia virus vaccine taught by Scholl et al. was not "presently available" as of the effective filing date of the O'Donnell patents, please note the recombinant vaccinia virus used by Scholl was in fact available at least as early as 1996, see reference 9 on page 580 of the Scholl et al. paper, and that recombinant vaccinia viruses encoding antigens or cytokines were known and used as of 1987, see reference 13 on page 580 in particular. Thus, while the exact vaccinia virus used in the Scholl reference may not have been made until the mid 1990's, recombinant vaccinia viruses were certainly known and in use in 1987 and therefore clearly qualify as one of the "presently available" vaccines referred to by O'Donnell.

The applicant also argues that the biochemistry of vaccinia virus versus mycobacterium affects the generation of immunologic responses to antigen and specifically MUC1. The applicant states that MUC1 protein expressed by BCG is not glycosylated and thus resembles the form of MUC1 specific for malignant breast cancer, whereas the MUC1 expressed by vaccinia virus is

glycosylated and resembles the benign form of MUC1. The applicant therefore argues that expression of a glycosylated form of MUC1 by a virus could not elicit an immunologic response specific for a tumor antigen. This argument is not persuasive since Scholl et al. clearly teaches that MUC1 expressed by a vaccinia virus is in fact capable of generating therapeutic MUC1-specific CTL *in vivo* in breast cancer patients (Scholl et al., page 570, and pages 575-576, Figures 3-4).

Thus, based on the advantages of BCG vaccines over other known vaccine systems including vaccinia virus, and the teachings of O'Donnell that BCG can be engineered to express an antigen and a cytokine to treat cancer, it would have been *prima facie* obvious to the skilled artisan to substitute a recombinant BCG for vaccinia virus in the method of treating cancer taught by Scholl et al. The skilled artisan would further have had a reasonable expectation of success in modifying the BCG-IL-2 vector taught by O'Donnell et al. to include a MUC-1 antigen sequence operatively linked to the hsp70 promoter in view of the detailed teachings in O-Donnell et al. for making recombinant BCG encoding antigens and cytokines. In addition, the skilled artisan would have had a reasonable expectation of success in generating therapeutic anti-MUC-1 immune responses using a recombinant BCG which expresses MUC-1 and IL-2 based on the proven efficacy of combined MUC-1 and IL-2 cancer therapy as taught by Scholl, and the successful use of BCG vaccines to generate antigen-specific immune responses taught by O'Donnell, '465 or '632.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 872-9306.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER